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1. AGENCY USE ONLY (Leave blank)

2. REPORT DATE
10 May 19943. REPORT TYPE AND DATES COVERED
Technical Report

4. TITLE AND SUBTITLE

Enantiomeric Separation of Chiral [α -(1-Naphthyl)
Ethyl]Ammonium Perchlorate by Silica Gel-bound
Chiral Pyridino-18-Crown-6 Ligands

5. FUNDING NUMBERS

N00014-91-J-1710
R & T Code 313p002

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8. PERFORMING ORGANIZATION
REPORT NUMBER

Technical Report No. 27

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)

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Office of Naval Research
800 North Quincy Street
Arlington, VA 22217-5000

10. SPONSORING/MONITORING
AGENCY REPORT NUMBER

N/A

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 words)

The separation of [α -(1-naphthyl)ethyl]ammonium perchlorate (NapEt) into its (R) and (S) forms using silica gel-bound dimethylpyridino-18-crown-6 ligand [(S,S)-1] with methanol as an eluent is reported. We also report the synthesis of a new silica gel-bound diphenyl-substituted pyridino-18-crown-6 ligand [(R,R)-2] by the following reactions. Dimethyl chelidamate (7) was first alkylated with 11-iodoundec-1-ene (6) on the phenolic oxygen and the resulting ether diester was reduced to form 4-undecenyl-oxy-2,6-pyridinedimethanol (8). Tosylation of 8 gave ditosylate 9 which was cyclized with (R,R)-diphenyl-substituted tetraethylene glycol [(R,R)-10] to form crown (R,R)-11. Ligand (R,R)-11 was treated with triethoxysilane using a platinum catalyst. The resulting chiral crown-substituted triethoxysilane, (R,R)-12, was reacted with silica gel in toluene at 90° to attach the ligand to silica gel. The results of the separation of (R)- and (S)-NapEt using new silica gel-bound crown (R,R)-2 with methanol as the eluent are also presented.

14. SUBJECT TERMS

400222-94-16280



15. NUMBER OF PAGES

16. PRICE CODE
N/A17. SECURITY CLASSIFICATION
OF REPORT

Unclassified

18. SECURITY CLASSIFICATION
OF THIS PAGE

Unclassified

19. SECURITY CLASSIFICATION
OF ABSTRACT

Unclassified

20. LIMITATION OF ABSTRACT

UL

94 6 1 005

OFFICE OF NAVAL RESEARCH

Grant N00014-91-J-1710

R&T Code 313p002

TECHNICAL REPORT NO. 27

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by

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May 11, 1994

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DTIC	TAB <input type="checkbox"/>
Unannounced <input type="checkbox"/>	
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ENANTIOMERIC SEPARATION OF CHIRAL [α -(1-NAPHTHYL)ETHYL]AMMONIUM PERCHLORATE BY SILICA GEL-BOUND CHIRAL PYRIDINO-18-CROWN-6 LIGANDS

P. Huszthy, J.S. Bradshaw, A.V. Bordunov and R.M. Izatt

Abstract

The separation of [α -(1-naphthyl)ethyl]ammonium perchlorate (NapEt) into its (*R*) and (*S*) forms using silica gel-bound dimethylpyridino-18-crown-6 ligand [(*S,S*)-1] with methanol as an eluent is reported. We also report the synthesis of a new silica gel-bound diphenyl-substituted pyridino-18-crown-6 ligand [(*R,R*)-2] by the following reactions. Dimethyl chelidamate (7) was first alkylated with 11-iodoundec-1-ene (6) on the phenolic oxygen and the resulting ether diester was reduced to form 4-undecenyoxy-2,6-pyridinedimethanol (8). Tosylation of 8 gave ditosylate 9 which was cyclized with (*R,R*)-diphenyl-substituted tetraethylene glycol [(*R,R*)-10] to form crown (*R,R*)-11. Ligand (*R,R*)-11 was treated with triethoxysilane using a platinum catalyst. The resulting chiral crown-substituted triethoxysilane, (*R,R*)-12, was reacted with silica gel in toluene at 90° to attach the ligand to silica gel. The results of the separation of (*R*)- and (*S*)-NapEt using new silica gel-bound crown (*R,R*)-2 with methanol as the eluent are also presented.

Introduction

In continuation of our studies on enantiomeric recognition of chiral organic ammonium salts by chiral pyridino-18-crown-6 ligands [1-7], we have studied the enantiomeric separation of chiral organic ammonium salts by chiral pyridino-18-crown-6 ligands covalently bonded to silica gel [8]. One and a half decades ago, Cram and coworkers published their pioneering paper [9] on the separation of the enantiomers of several racemic organic ammonium salts using a silica gel-bound chiral bis(binaphthyl)-22-crown-6 ligand. After covalently attaching the chiral ligand to silica gel they treated the adsorbent with an excess of chlorotrimethylsilane to form a less polar material. This treatment reduced tailing and gave better separations on their solid stationary phase. They used a mobile phase consisting of chloroform or dichloromethane solutions of the racemic ammonium salts and 18-crown-6, ethanol, or 2-propanol as carriers [9]. Our preliminary results of the separation of [α -(1-naphthyl)ethyl]ammonium perchlorate (NapEt) into its (*R*) and (*S*) forms using silica gel-bound chiral crown (*S,S*)-1 (see Figure 1) with acetone/methanol (7/3)(v/v) as the eluent were not completely satisfactory [8].

In this paper, we report a good, almost base-line separation of NapEt into its (*R*) and (*S*) forms using silica gel-bound chiral crown (*S,S*)-1 with methanol as the eluent. We also report the use of (*R,R*)-2 for the separation of the enantiomers of NapEt. Silica gel-bound chiral crown (*R,R*)-2 differs from silica gel-bound chiral crown (*S,S*)-1 in two features: a) (*R,R*)-2 has a longer connecting arm to silica gel by seven carbon atoms; and b) instead of two methyl substituents, (*R,R*)-2 contains two phenyl moieties at the chiral centers. These changes were made because silica gel-bound chiral stationary phases eleven carbon atoms removed from the support were very effective for chiral solute separations [10-13], and second, the substitution of two methyl groups in (*S,S*)-1 by two phenyl groups to form (*R,R*)-2 should improve chiral recognition and subsequently chiral separation.

Results and Discussion

The separation of (*R*)- and (*S*)-NapEt using silica gel-bound (*S,S*)-1 is shown in Figure 2. This separation study was carried out in a manner similar to that reported [8]. Very concentrated methanol solution of racemic NapEt was placed on a column containing (*S,S*)-1. The

eluent was methanol. Methanol was used because it allows for a good separation of enantiomers, reduces greatly the time for a separation, and reduces tailing to a great extent. The amounts of (*R*)- and (*S*)-NapEt in each fraction were determined by HPLC using the *N*-acetyl derivatives of (*R*)- and (*S*)-NapEt [8]. Because (*S,S*)-1 interacts more strongly with (*R*)-NapEt, (*S*)-NapEt passes through the column first and (*R*)-NapEt last as observed in Figure 2.

The separation of (*R*)- and (*S*)-NapEt using silica gel-bound (*R,R*)-2 is shown in Figure 3. This separation was performed as described above using (*S,S*)-1. Since the parent chiral diphenyl-substituted crown [(*R,R*)-4] exhibits less recognition for the enantiomers of NapEt as mentioned above, the separation using (*R,R*)-2 was not as good as that using (*S,S*)-1. As shown in Figure 3, (*R*)-NapEt elutes first from the column because (*R,R*)-2 interacts with (*S*)-NapEt more strongly. Although a clean separation of enantiomers by (*R,R*)-2 was not achieved in this one experiment, it is clear that recognition did take place. Another solvent system could be found and a better separation by (*R,R*)-2.

Experimental

Separation of R-(+)-and S-(-)-Isomers of NapEt on (S,S)-1 with Methanol as Eluent

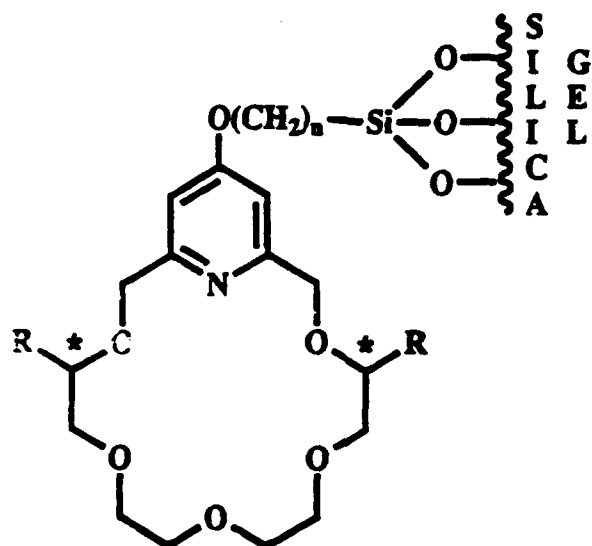
This separation was carried out in the same manner using the same column filled with 4.2 g of (*S,S*)-1 as reported [8] with the following exemptions: a) prior to separation, 50 ml of 1/4 (v/v) triethylamine/methanol and then 100 ml of pure methanol were passed through the column and b) instead of a 3/7 (v/v) methanol/acetone mixture, pure methanol was used as an eluent. The flow rate was 0.048 ml/min. The calculated [8] concentrations of (*R*)- and (*S*)-NapEt were plotted versus the ml of eluent as shown in Figure 2.

Separation of R-(+)- and S-(-) Isomers of NapEt on (R,R)-2 with Methanol as Eluent

This separation was carried out in the same manner as described above for (*S,S*)-1 using (*R,R*)-2 silica gel-bound chiral diphenylpyridino-18-crown-6 with pure methanol as an eluent. The flow rate in this case was 0.017 ml/min. The calculated [8] concentrations of (*R*)- and (*S*)-NapEt were plotted versus the ml of eluent as shown in Figure 3.

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(*S,S*)-1, $R = \text{CH}_3$, $n = 3$
 (*R,R*)-2, $R = \text{C}_6\text{H}_5$, $n = 11$

Fig. 1. Silica gel-bound chiral
 pyridino-18-crown-6 ligands

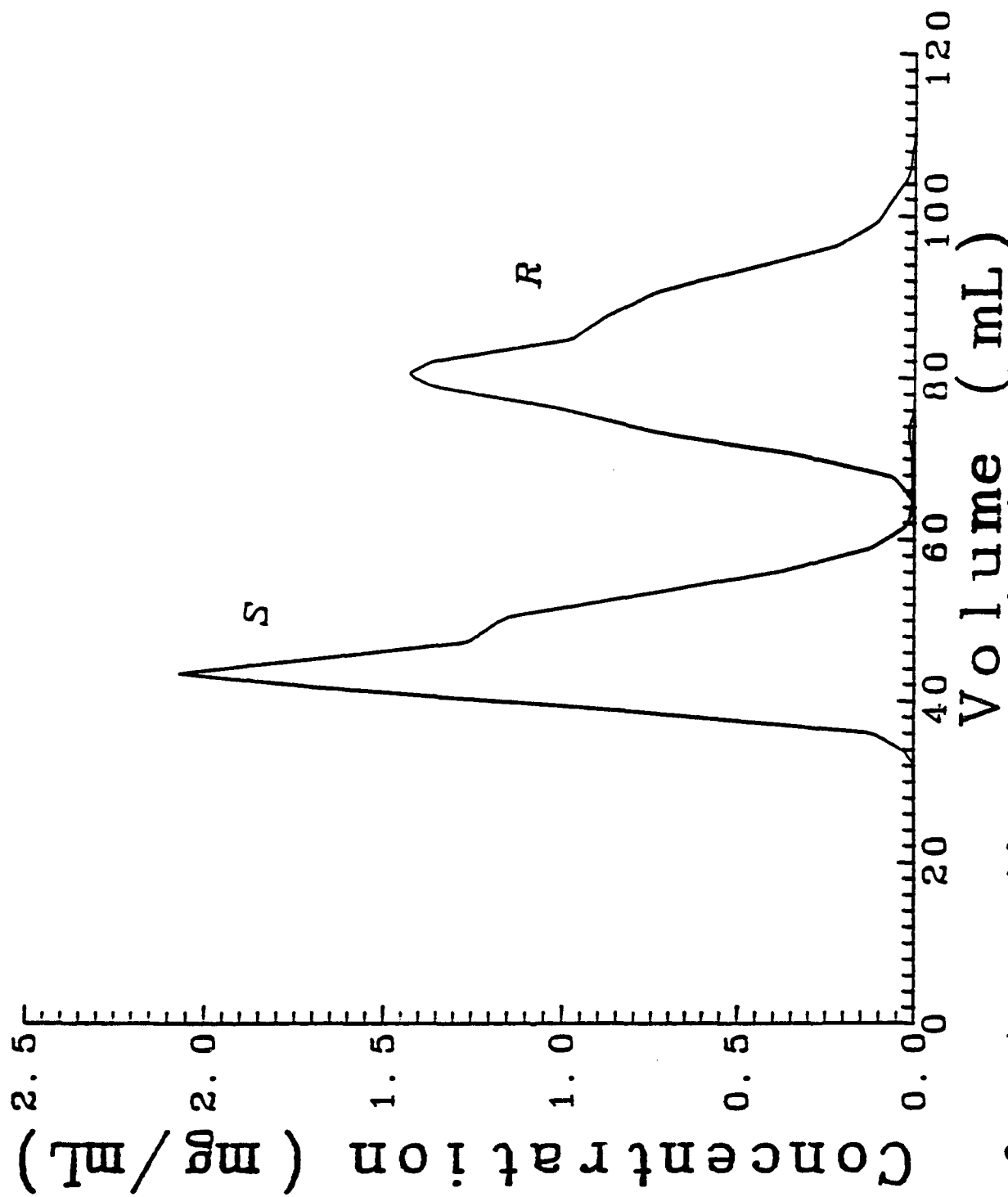


Figure 2. A smooth curve showing the separation of (R)- and (S)-NapEt on (S, S)-1 using methanol as eluant.

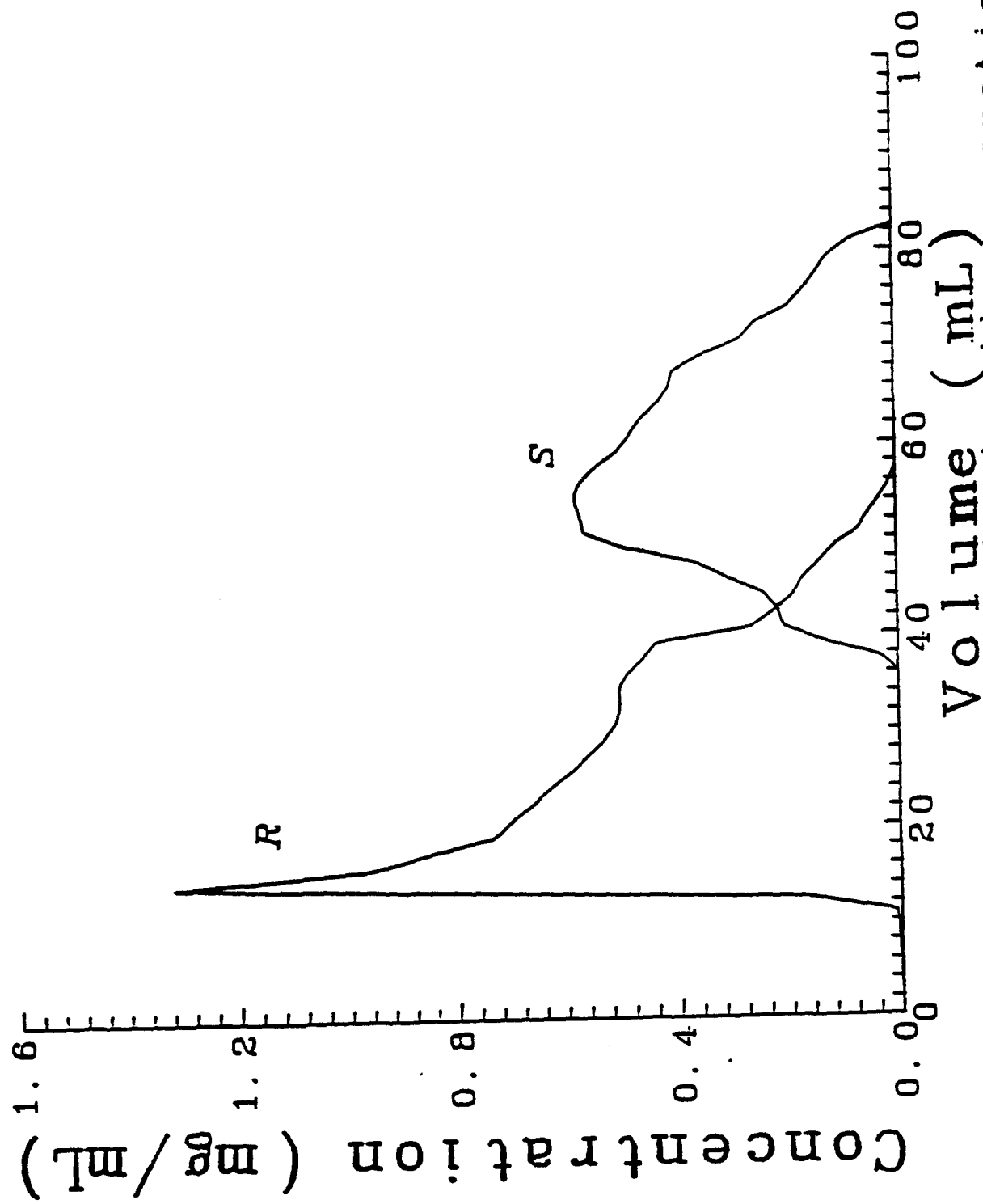


Figure 3. A smooth curve showing the separation of (R) - and (S) -NapEt on (S, S) -2 using methanol as eluant.